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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,762	12/27/2005	Massimo Ferrari	207,385	8763

7590 07/20/2009  
Jay S Cinamon  
Abelman Frayne & Schwab  
10th Floor  
666 Third Avenue  
New York, NY 10017

EXAMINER
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MABRY, JOHN

ART UNIT	PAPER NUMBER
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1625

MAIL DATE	DELIVERY MODE
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07/20/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/562,762	FERRARI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 26-43 and 47-49 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-43 and 47-49 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

***Response to Applicant's Remarks***

Applicant's response on April 22, 2009 filed in response to the Office Action dated October 6, 2008 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

***Status of the Claims***

Claims 26-43 and 47-49 are pending and rejected.

Claims 47-49 are new.

Claims 1-25 and 44-46 have been cancelled.

***Claim Rejections - 35 USC § 103***

Rejected claims under 35 U.S.C. 103(a) as being unpatentable over Jones et al (US 4,358,593) in view of Jones et al (EP62503) and in further view of Alt (US 5,523,416) have been withdrawn due to reconsideration by Examiner.

Claims 26-46 and 47-49 rejections are maintained under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684).

For purposes of convenience, the rejection is repeated below:

The instant application claims a process for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) to

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make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I).

### **Scope & Content of Prior Art MPEP 2141.01**

Alt describes a process as illustrated in Scheme III (columns 5/6) for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) (R=C1-C6 alkyl, column 2, lines 8-9 and see "Dealkylation" in column 7) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) (see "Reprotection" in bottom of column 7 column 8, lines 1-5). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is

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acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) then isolating the crude product (see "Acylation" in column 9, lines 22-23, lines 37-41). The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I) (see "Deprotection of Reprotected Dihydroxythiophenes" in bottom of column 10 - column 11, lines 1-5 and lines 28-39).

***Differences between Prior Art & the Claims MPEP 2141.02***

Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI).

Additionally, the instant application describes the purity (and impurities) of products in claimed process.

***Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413***

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by Alt. The procedure, steps of synthesis and reactions conditions are all described that would motivate one of ordinary skill in the art to make minor and obvious experimental adjustment in order to achieve high yields and high purity of desire product, (I).

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents, interchanging a particular acid and/or base, not isolating intermediates, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re Mostovych*, Weber, Mitchell and Aulbach, 144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

Applicant argues Examiner's motivation to cite another reference of Alt (US 5,512,684) when it "stems from a continuation of the application that led to Atl '416." Firstly, Examiner has the right to choose any prior he deems the most relevant in regards to the instantly claimed invention. Secondly, Examiner cited new reference

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simply because he believed it to be proper and more relevant prior art. This new rejection was proper in view of RCE filed on September 17, 2008.

As clearly stated in previous Office Action, the differences between prior art and the claims are as follow:

Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI). Additionally, the instant application describes the purity (and impurities) of products in claimed process.

Applicant argues that Examiner does not provide any motivation as to why one of ordinary skill in the art avoid the step of isolating 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) and proceeding to the final product (I) *in situ* by addition of a strong acid, in particularly hydrochloric acid.

As stated in previous Office Action, it is well within the purview of the skilled artisan in the relevant art to reduce steps in order to achieve the desired product faster and in higher yields.

Dorwald clearly states that in the design of an organic molecule, a synthetic chemist would need to analyze *"the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity"* – see page 2 under 1.2 Synthesis Design.

Again, an artisan of ordinary skill, in this case, an organic chemist, would be motivated to take the prior art of Alt '684 and reduce the step of isolation of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) in order to achieve the final product (I) in greater yield and higher purity.

Note: The reference of Dorwald was added only to address Applicant's arguments in regards to motivation.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### ***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/John Mabry/  
Examiner  
Art Unit 1625

/Rita J. Desai/  
Primary Examiner, Art Unit 1625